Diabetes progression modelling of competing risks of long-term complications and mortality using Swedish registry data

Hanna Kunina, Maria C. Kjellsson

Pharmacometric Research Group, Department of Pharmaceutical Biosciences, Uppsala University

Introduction and Objectives

Recent evidence suggests that patients suffering from type 2 diabetes mellitus (T2DM), may have varying degrees of long-term complications risks, depending on the presence and severity of comorbidities[1]. T2DM is associated with disabling and potentially life-threatening micro- and macrovascular complications, and diseases such as chronic kidney disease (CKD) and cardiovascular disease (CVD) are of paramount interest[2].

The aim of this project was to develop a multistate model for competing risks using data from the Swedish National Diabetes Registry (NDR) and characterize the impact of covariates on the competing risks.

Materials and Methods

Adult patients with T2DM, registered in National Diabetes Register (NDR) between 2005 and 2013, without prior events of CKD and CVD and with record of pre-specified covariates were included in the study. Disease progression was described by a multistate, competing risks, Markov model with five clinical states that an individual can occupy at a given time point [3] (*Figure 1*). A competing risk is an event which occurrence precludes or may modify the probability of the onset of another event of interest.

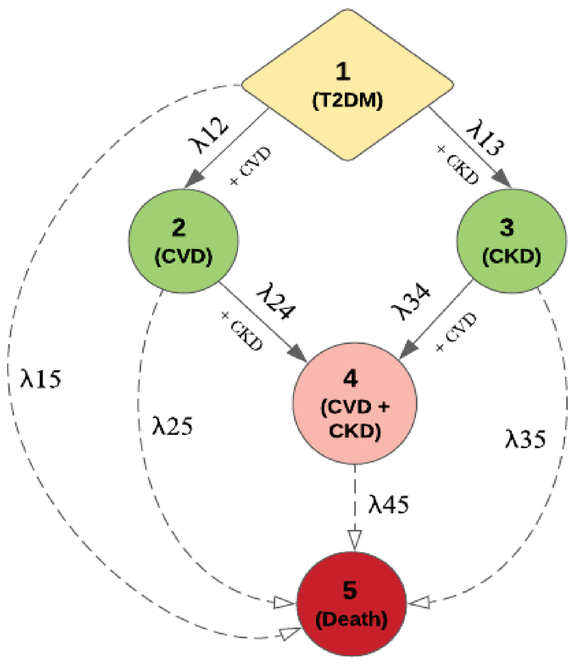

Figure 1. Structural model

All subjects started from the initial state 1 (T2DM) without comorbidities and moved towards the terminal state 5 (death) either through intermediate states 2 (CVD), 3 (CKD), or 4 (CVD+CKD) or directly.

Cumulative hazards (λs) were used to describe the transition intensities[3].

Time-invariant covariates were included based on prior knowledge and the covariate relationship was characterized. External validation was performed by data-splitting.

Model development and qualification

Whole dataset
105263 patients (100%)

Exploratory data analysis
- Study population characteristics
- Data management

Training dataset
78951 patient (75%)

Basic structural population model development
- NLMEM
- FOCE, MAX LIKE

Training dataset
78951 patient (75%)

Covariate model development
- Time-invariant covariates relationship characterization
- Time-variant covariates exploration using LRT*

Final model evaluation

Training dataset 78951 patient (75%)
- Internal validation (VPC, LRT*)

Test dataset 26312 patients (25%)
- External validation

*LRT – likelihood-ratio test

Table 1. Significant pre-specified covariates

CVD	CKD	Median	Range
BMI		29.32	13.42 – 50
Blood pressure		135/80	80 - 250 /40 – 130
HbA1c		51	26 - 145
	SEX	-	M (53.79 %) F (46.21 %)

Gompertz-Makeham equation

$$\lambda = \alpha + \beta \cdot e^{(\kappa \cdot (age - \theta))}$$

where the intercept parameter α, the scale parameter β and the shape parameter κ were function of sex and age

Results and Discussion

The final model described the semi-competing terminal process of death and the two competing non-terminal processes of developing CVD and CKD during the follow-up period *(Figure 3).* Body mass index (BMI), glycated haemoglobin (HbA1c), systolic blood pressure and sex were found to have significant effect on the risks and transition intensity from state 1 to state 2 and 3 *(Table 1).* Final model parameter estimates with residual squared errors (RSE) are presented in *Table 2.* External validation showed a well-predictive model (*Figure 4a and 4b*).

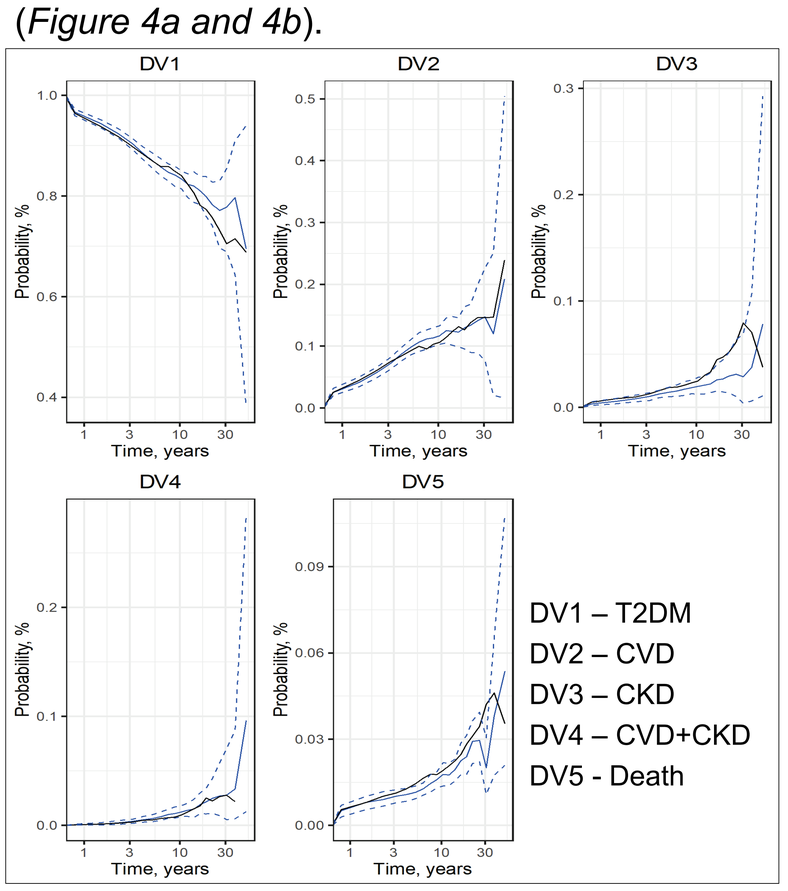

Figure 3. Visual predictive check (VPC) of the final model.

Solid black line represents the median of the observed data. Solid blue line represents the median of the simulated data. Dashed blue lines represent 97.5th and 2.5th percentiles of the PI of the simulated data. NB! x-axis is logged

Parameter	Estimates	RSE(%)
1/α12	1900	69.47
β12	0.000207	12.46
κ12	0.085	1.91
MbAS13 (24)	7.9	5.60
GAM12	35.9	2.35
BMI12	-3.87	28.42
SYS12	-0.0912	81.8
HbA1c12	-3.16	39.24
1/α13	3270	25.05
β13	2.4E-06	16.88
κ13	0.108	2.01
MbAS12 (34)	1E-06	FIX
MtAS15	7.18	1.99
MtAS25	-1.9	14.47
MtAS35	-2.37	22.11
MtAS45	-10.2	5.57
BMI13	-4.95	11.74
SYS13	-6.04	17.55
SEX13	0.168	161.9

Table 2. Final model parameter estimates with their residual square errors (RSE (%)).

MtAS – mortality age shift (years). MbAS – morbidity age shift (years)

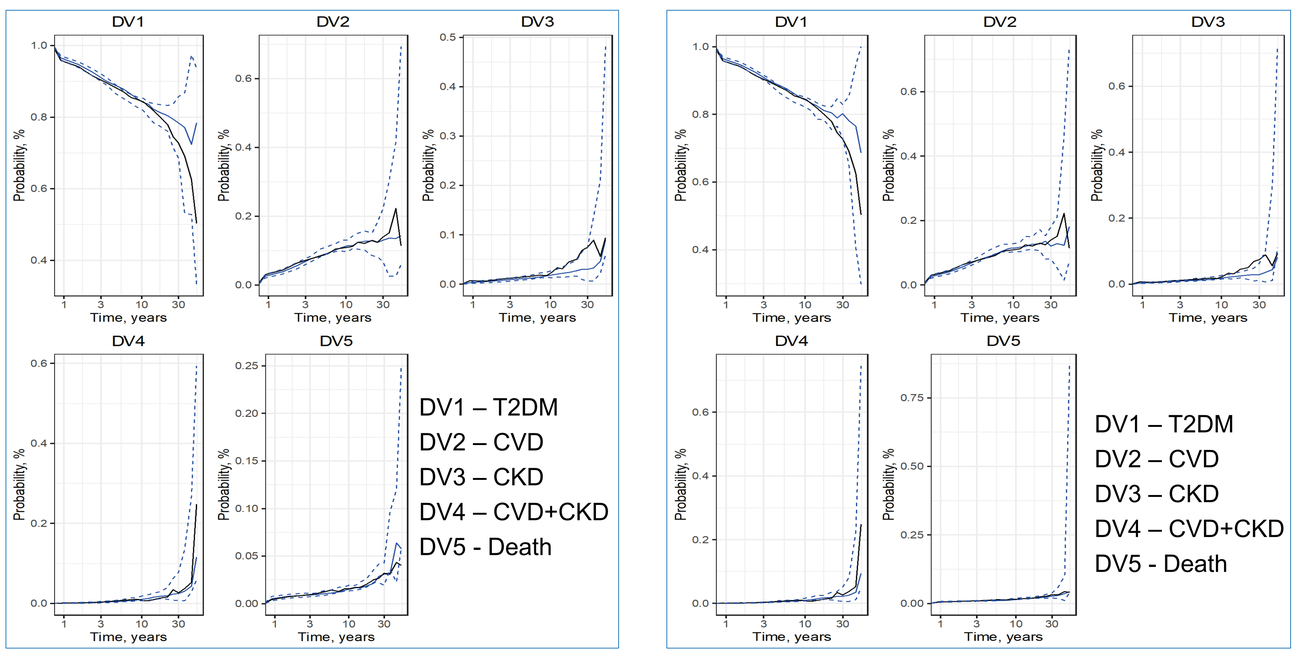

Figure 4a and 4b. External validation

VPC of the final model applied to test dataset. NB! x-axis is logged

Conclusion

A multi-state model for competing risks of T2DM long-term complications was successfully developed. This model adequately described the diabetic disease progression in the Swedish patient population. The magnitude of estimated covariate effects was reasonable and meaningful. Future work involves assessment of the treatment impact on the risk of comorbidities and mortality.

References

[1] Parrinello, CM et al. *Risk prediction of major complications in individuals with diabetes: the Atherosclerosis Risk in Communities Study*. Diabetes, obesity & metabolism (2016), 18(9), 899-906.

[2] Chawla, A et al. *Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum.* Indian journal of endocrinology and metabolism (2016), 20(4), 546-51.

[3] Ibrahim, Moustafa M. A (2019). *Pharmacometric evaluation and improvement of models and study designs - applied in diabetes.* Uppsala: Acta Universitatis Upsaliensis. Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Pharmacy, 264. p. 75. Uppsala. ISBN: 978-91-513-0518-9.